Published in final edited form as:

Pediatr Neurol. 2013 July ; 49(1): 50–53. doi:10.1016/j.pediatrneurol.2013.03.008.

The Perils of SNP Microarray Testing: Uncovering Unexpected Consanguinity

Beth A. Tarini, MD^{*,1}, Laura Konczal, MD^{*,2}, Aaron J. Goldenberg, PhD, MPH³, Edward B. Goldman, JD⁴, and Shawn E. McCandless, MD²

¹Child Health Evaluation and Research (CHEAR) Unit, Department of Pediatrics, University of Michigan, Ann Arbor, MI

²Department of Genetics and Genome Sciences, Case Western Reserve University and Center for Human Genetics, University Hospitals Case Medical Center, Cleveland, OH

³Department of Bioethics and Center for Genetic Research Ethics and Law, Case Western Reserve University School of Medicine, Cleveland, OH

⁴Department of Obstetrics and Gynecology, University of Michigan, Ann Arbor, MI

Abstract

Background—While single nucleotide polymorphism (SNP) chromosomal microarrays identify areas of small genetic deletions/duplications, they can also reveal regions of homozygosity indicative of consanguinity. As more non-geneticists order SNP microarrays, they must prepare for the potential ethical, legal and social issues that result from revelation of unanticipated consanguinity.

Patient—An infant with multiple congenital anomalies underwent SNP microarray testing.

Results—The results of the SNP microarray revealed several large regions of homozygosity that indicated identity by descent most consistent with a second or third degree relative mating (e.g., uncle/ niece, half brother/sister, first cousins). Mother was not aware of the test's potential to reveal consanguinity. When informed of the test results, she reluctantly admitted to being raped by her half-brother around the time of conception.

© 2013 Elsevier Inc. All rights reserved.

Address Correspondence to: Shawn E. McCandless MD, Center for Human Genetics, 11100 Euclid Avenue, Cleveland OH, 44106, [shawn.mccandless@case.edu], 216-844-3936.

*Co-First authors: These authors contributed equally to the creation of this work.

Financial Disclosure The authors have no relevant financial relationships to disclose.

Conflict of Interest: The authors have no conflicts of interest to disclose.

Contributors statement: Laura Konczal: Dr. Konczal conceptualized the study, is the physician who saw the patient/ family in the case report, developed the case reports, drafted the initial manuscript, and approved the final manuscript as submitted.

Beth A. Tarini: Dr. Tarini conceptualized the study, drafted the initial manuscript, and approved the final manuscript as submitted.

Aaron J. Goldenberg: Dr. Goldenberg contributed to the discussion, critically reviewed and revised the manuscript, and approved the final manuscript as submitted.

Edward B. Goldman: Professor Goldman contributed to the discussion, critically reviewed and revised the manuscript, and approved the final manuscript as submitted.

Shawn E. McCandless: Dr. McCandless conceptualized the study, developed the case reports, drafted the initial manuscript, and approved the final manuscript as submitted.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Conclusions—During the pre-testing consent process, providers should inform parents that SNP microarray testing could reveal consanguinity. Providers must also understand the psychological implications, as well as the legal and moral obligations, that accompany SNP microarray results that indicate consanguinity.

Keywords

SNP microarray; informed consent; consanguinity; genetic counseling

Introduction

Single nucleotide polymorphism (SNP) chromosomal microarray technology is used to assess the genome of individual patients for copy number variants (often referred to as CNVs) – regions of genetic deletions and/or duplications, especially those too small to be detected by prior methods. The use of SNPs adds a level of detail beyond what is possible with hybridization techniques (oligonucleotide probes, or short pieces of DNA that hybridize with DNA from the patient sample) and highlights regions of homozygosity that can help identify the causative genetic change for autosomal recessive inherited conditions, as shared genetic material resulting from consanguinity increases the risk of these disorders.¹ SNP microarrays may also uncover regions of homozygosity suggesting consanguinity caused by mating between related persons or by partners coming from an inbred population. While consanguineous relationships are accepted in some cultures, they may not be in others. In some cases, such evidence of consanguinity may indicate that a crime has been committed –as in the case of an incestuous relationship or a pregnant minor.²

An unexpected revelation of consanguinity through SNP microarray testing can provoke emotional, psychological and/or legal issues for affected patients and families. Herein we present a clinical case that illustrates some of these controversial issues and then discuss their implications, which will be of interest to pediatric neurologists who may increasingly order SNP microarrays as part of routine clinical evaluations for developmental delay and autism.²⁻⁵

Clinical Case

An infant was evaluated for multiple congenital anomalies. The child was born to a reportedly non-consanguineous married couple with no family history of birth defects, learning disabilities, or miscarriages. Careful medical evaluation did not suggest a diagnosis of a specific genetic syndrome. A SNP microarray demonstrated several large regions of homozygosity that indicated that the areas were identical by descent (both copies inherited from a common ancestor) and were most consistent with a second or third-degree relative mating (e.g., uncle/niece, half brother/sister, first cousins). In practical terms, this test revealed unsuspected consanguinity, specifically incest.

When the information was shared confidentially with the mother, a competent adult, she reluctantly admitted to being raped by her half brother (a second degree relative) around the time of conception. She reported that she was safe and no longer in contact with him. She informed the medical providers that she didn't intend to share this information with her husband, who believed that he was the father, nor with other relatives. She also did not wish to report the rape to authorities and asked that this information not be shared or documented in the medical record. She also declined a referral for counseling.

The family neither returned to clinic nor responded to follow-up phone calls. The following year, the mother left the child and her husband (who believes he is the child's father), and

her husband's mother (paternal grandmother) was appointed temporary guardian of the child. She has since requested the SNP microarray results.

Discussion

This case raises numerous ethical, legal and psychosocial issues for individuals, their families and the ordering healthcare provider that undergo SNP microarray testing.

Identity and Familial Values

While this case focuses on a specific instance of significant consanguinity – namely the incestuous mating between second-degree relatives – healthcare providers should be aware that not all consanguinity represents incest and that cultural acceptance of consanguinity varies.⁶ In some cultures, mating between individuals known to be related is encouraged and accepted, while in “closed societies” with a high coefficient of inbreeding (an estimate of the proportion of shared alleles, or genetic sequence variants, between individuals in a community),⁷ the degree of relatedness may be unknown to apparently unrelated couples who share more genetic material than they realize.⁸

Even if consanguinity is part of their culture or community, individuals may not want to acknowledge it within their own family. Fears of stigmatization or discrimination can be a perceived risk for families undergoing genetic testing that could reveal consanguinity.⁹ This situation can be compounded for families who have relocated to new and distant communities where consanguinity may lead to unfavorable judgment. Cultural/religious values may also restrict options available for these couples.¹⁰ For example, in some faith traditions, couples can neither engage in pregnancy prevention nor divorce, nor terminate future pregnancies because these actions are religiously prohibited. Given the potential threats of this information to individual and familial identity, families in these situations should be offered resources for emotional and psychological support. In such cases the information identified by the SNP microarray must be discussed with the family as it identifies them as being at increased risk for having children with genetic abnormalities in future pregnancies.

In these discussions, sensitivity to the parents' current social and emotional needs is essential. For example, it may be adequate to tell the parents that they share a significant degree of genetic material, possibly related to a relative lack of migration in or out of the community from which they come, without explicitly stating that they share enough genetic material to be close relatives. Further, clinicians reporting such findings, whether in a laboratory report or a clinical note, should choose their words carefully to avoid making presumptions about the nature of the parents' relationship based solely on the pattern of the shared genetic material. In general, a few long stretches of shared genetic material are more suggestive of a familial relationship than is a similar total amount of shared material made up of many small and widely distributed segments. If there is not significant clinical utility to stating in the medical record the most likely mechanism to explain the pattern of shared material, it may be best to merely report its presence in quantitative terms (e.g., “approximately 12% of the genome has a common origin”) rather than in terms of presumed relationship of the parents (e.g., “the shared alleles are at the level expected in parents who are first cousins”).

Informed Consent

This case illustrates the need to inform parents during the pre-testing consent process that certain tests can reveal consanguinity. Aside from discussions of what details a provider must disclose to families about results that reveal consanguinity, a more salient obligation

involves the consent process prior to undergoing SNP microarray testing. Informed consent for testing for heritable diseases is not federally mandated, but is required by law in at least 12 states and by many molecular genetic laboratories prior to testing.¹¹ Informed consent processes for SNP microarrays should address many of the same issues involved in counseling prior to DNA sequencing, along with the special concerns raised by the genomic approach (one of which is the potential to recognize consanguinity even without parental testing). Healthcare providers should provide enough detailed pretesting information to allow the patient to understand possible test findings and their implications. Providers should also include opportunities for patients to discuss their questions or concerns about test implications. Given her history of incestuous rape, the mother described above stated that she may have declined testing had she been aware that the test results could uncover this information. If a parent objects to testing because of fear of uncovering consanguinity, providers should consider whether offering testing with limited disclosure of results is possible (either to patients/ family members or in the medical record).

Providers also must understand the methods of the assay that they intend to use. For example, microarrays that use comparative genomic hybridization, like oligonucleotide microarrays, do not identify regions of homozygosity. In contrast, sequence based testing, whether a SNP microarray that sequences individual discrete areas of known variability, or gene sequencing (whole exome or whole genome sequencing) can identify homozygosity.

Legal and Moral Responsibility

This case raises questions about the clinician's legal and moral obligations when SNP microarray testing reveals a degree of homozygosity indicative of an incestuous relationship. If the physician discovers a consensual incestuous relationship among competent adults, he/she is not legally required to report it. If the sexual relationship is not consensual (i.e., rape), incestuous or otherwise, but the victim is a competent adult who does not want to report a crime to authorities, the physician is also not legally obligated to disclose this information, with exceptions in a few states.¹² However, if one of the individuals involved in the incestuous relationship were a minor or an incompetent adult – the law requires that the physician report suspected statutory rape, child abuse or neglect.¹³

There is a possibility that by providing this information in the consent process before testing, a parent might avoid testing that would reveal a crime. The competing duties here are complex. It is not satisfactory to ignore these issues simply by failing to disclose. If a crime against a minor or incompetent adult has been committed, physicians are obligated to report it. With the physician's primary duty to protect the minor patient, the appropriate response to parental refusal of testing that could reveal consanguinity is to have a respectful discussion about the reasons for the parents' concern. This discussion by itself may raise concerns that prompt the physician to report the case to the appropriate authorities.

Privacy Requirements

Families may have significant concerns about privacy after revelation of unexpected consanguinity. In this case the mother requested that information discussed not be placed in the medical record. Since the medical chart contains relevant diagnostic information protected by HIPAA and state confidentiality laws, it could be argued that the rape of the mother may not be necessary clinical information for the child's chart. This is a decision usually left to the clinician, who should consider the possibility that a future provider may inadvertently disclose the information in a way that is unacceptable to the parent. In these cases, privacy is important since the Genetic Information Non-Discrimination Act (GINA) is meant to protect the misuse of health related genetic testing results, but does not address stigmatization in the family or community if consanguinity becomes publically known.¹⁴

The situation becomes even more complex when others have a legal right to information contained within a minor's medical record. As described in this case, the husband's mother gained temporary legal guardianship of the child a year after the mother disclosed her rape. In the state that this case occurred, only the permanent legal guardian has a right to information contained in the child's medical record, which would allow her to discover that she and her son are not biologically related to the child for whom she has taken legal responsibility (information that the biological mother had requested not be disclosed). Since the rape of the mother and the identity of the biological father is not relevant to the child's medical care or diagnosis, the content of the SNP microarray report describing the shared material, but not the likely mechanism, may be the only information that is legally required to disclose to the guardian. The physician is forced to make a decision about how much information is legally permissible and necessary to share to ensure appropriate medical care for the child in the setting of a temporary guardian.

Conclusion

Most neurologists, and many other healthcare providers, have come to recognize that mis-assigned paternity is a surprisingly common finding when performing sequence-based genetic tests in children and their parents. These providers are careful to tactfully explain this to parents before testing is done to avoid surprises and stress when results come back. As SNP microarrays and other assays (e.g., whole exome and genome sequencing) replace older tests as first line evaluations of children with developmental delay and/or autism, ²⁻⁴ pediatric neurology providers now must educate themselves about the need for informed consent and the potential revelation of unexpected consanguinity. Given the complexity of these issues, non-genetics providers may wish to consider consultation with professionals trained to interpret and explain these test results (i.e. geneticists and genetic counselors) prior to ordering SNP microarrays.

The content herein is solely the responsibility of the authors and does not represent the official views of the National Institute of Diabetes and Digestive and Kidney Diseases, National Institute for Child Health and Human Development, National Human Genome Research Institute or National Institutes of Health.

Acknowledgments

Funding Source: Dr. Tarini is supported by a K23 Mentored Patient-Oriented Research Career Development Award from the National Institute for Child Health and Human Development (K23HD057994). Dr. Goldenberg is supported by the Center for Genetic Research Ethics & Law (P50HG003390) from the National Human Genome Research Institute. Dr. McCandless is supported by a K08 Mentored Clinical Scientist Career Development Award from the National Institute of Diabetes and Digestive and Kidney Diseases (K08DK074573).

References

1. Schaaf CP, Scott DA, Wiszniewska J, Beaudet AL. Identification of incestuous parental relationships by SNP-based DNA microarrays. *Lancet*. Feb 12; 2011 377(9765):555–556. [PubMed: 21315943]
2. Manning M, Hudgins L. Array-based technology and recommendations for utilization in medical genetics practice for detection of chromosomal abnormalities. *Genet Med* Nov. 2010; 12(11):742–745.
3. Schaefer GB, Mendelsohn NJ. Clinical genetics evaluation in identifying the etiology of autism spectrum disorders. *Genet Med* Apr. 2008; 10(4):301–305.
4. Shaffer LG. American College of Medical Genetics guideline on the cytogenetic evaluation of the individual with developmental delay or mental retardation. *Genet Med*. Nov-Dec;2005 7(9):650–654. [PubMed: 16301868]

5. Michelson DJ, Shevell MI, Sherr EH, Moeschler JB, Gropman AL, Ashwal S. Evidence report: Genetic and metabolic testing on children with global developmental delay: report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. *Neurology*. Oct 25; 2011 77(17):1629–1635. [PubMed: 21956720]
6. al-Gazali LI, Bener A, Abdulrazzaq YM, Micallef R, al-Khayat AI, Gaber T. Consanguineous marriages in the United Arab Emirates. *J Biosoc Sci* Oct. 1997; 29(4):491–497.
7. Bennett RL, Motulsky AG, Bittles A, Hudgins L, Uhrich S, Doyle DL, Silvey K, Scott CR, Cheng E, McGillivray B, Steiner RD, Olson D. Genetic Counseling and Screening of Consanguineous Couples and Their Offspring: Recommendations of the National Society of Genetic Counselors. *J Genet Couns*. 2002; 11(2):97–119.
8. Khlat M, Khoury M. Inbreeding and diseases: demographic, genetic, and epidemiologic perspectives. *Epidemiol Rev*. 1991; 13:28–41. [PubMed: 1765114]
9. Panter-Brick C. Parental responses to consanguinity and genetic disease in Saudi Arabia. *Social science & medicine*. 1991; 33(11):1295–1302. [PubMed: 1776043]
10. Bittles AH. The bases of western attitudes to consanguineous marriage. *Dev Med Child Neurol*. Feb; 2003 45(2):135–138. [PubMed: 12578240]
11. Chen B, Gagnon M, Shahangian S, Anderson NL, Howerton DA, Boone DJ. Good Laboratory Practices for Molecular Genetic Testing for Heritable Diseases and Conditions. *MMWR*. 2009; 58(RR06):1–29. [PubMed: 19521335]
12. Gupta M. Mandatory reporting laws and the emergency physician. *Ann Emerg Med* Mar. 2007; 49(3):369–376.
13. Child Welfare Information Gateway. Mandatory Reporters of Child Abuse and Neglect: Summary of State Laws. U.S. Department of Health and Human Services; 2010.
14. Genetic Information Nondiscrimination Act of 2008. 110th Cong, H R. 2008; 493

Abbreviations

SNP single nucleotide polymorphism